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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/978,633	11/25/97	RABBANI E	ENZ-53 DN

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EXAMINER	
SCHMIDT, M	

ART UNIT	PAPER NUMBER
1635	5

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Please find below and/or attached an Office communication concerning this application or pr ceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev. 2/95)

*U.S. GPO: 1998-437-638/80022

1- File Copy

Office Action Summary

Application No.	Applicant(s)
08/978,633	Rabbani et al.
Examiner	**Group Art Unit**
Schmidt	1635

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disp sition of Claims

☑ Claim(s) 2-24 and 245-302 is/are pending in the application.

Of the above claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☑ Claim(s) 2-24 and 245-302 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☑ Notice of Reference(s) Cited, PTO-892

☑ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Interview Summary, PTO-413

☐ Notice of Informal Patent Application, PTO-152

☐ Other _____

Office Action Summary

DETAILED ACTION

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures: Sequences in this specification and/or the claims are not referenced by sequence identifiers.

Double Patenting

2. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

3. Claims 2-24 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 2-24 of copending Application Nos.: 08/978,632, 08/978,636, 08/978,634, 08/978,635, 08/978,637, 08/978,638, 08/978,639, and 08/574,443. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or

improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claim 245 is provisionally rejected under the judicially created doctrine of double patenting over claims 22-24 of the instant application and of copending Application Nos. 08/978,632, 08/978,634, 08/978,635, 08/978,636, 08/978,637, and 08/978,638. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows:

There is only a slight difference in scope between claims 245 and 22-24 because claim 245 further claims an antibody bound to the hybridized polynucleotide sequence and further because all the limitations of claims 22-24 are encompassed by claim 245 as a single claim. Instant claim 245 essentially claims the same construct having a terminus comprising a polynucleotide tail hybridized to a complementary polynucleotide sequence where the construct is also bound non-ionically to an entity comprising a chemical modification or a ligand.

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending applications. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Claim Rejections - 35 USC § 112

6. Claims 2-21 and 256-260 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2-21 are indefinite because they depend from canceled claim 1. Therefore, claims 2-21 do not depend on any independent claim.

It is not clear what the metes and bounds are of the language "a specific complex" is in claims 256-260.

7. Claims 2-24 and 245-302 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The constructs taught in the claims 2-24 are broadly drawn to a multitude of possible nucleic acid based constructs for use in a cell to produce a product (and in any context, *in vivo* or *in vitro*), comprising: (1) the construct as linear or circular, (2) the construct as comprising 1,2 or 3 strands, (3) comprising a terminus, a polynucleotide tail which can hybridize, (4) composed of RNA or DNA or combinations, (5)containing chemically modified nucleotides or analogs, (6) containing non-nucleic acid entities composed of polymers or ligands or a combination, (7) further specifying the natural and synthetic polymers, the synthetic homo- or heteropolymer with a net charge, (8)the construct imparting a "further biological activity" by the modified nucleotide, analog, entity, ligand or combination of those, further defined as nuclease resistance, cell recognition, cell binding, and cellular or nuclear localization or a combination, (9) a ligand attached to one of the modified nucleotides, etc. of claim 1, further described as attached to a "segment" or "tail" of the construct , and further defined as being a macromolecule or small molecule or combination. Claims 22-24 describe a second construct "which when present in a cell produces a product, said construct being bound non-ionically to an entity comprising a chemical modification or a ligand."

Claims 245-254 are drawn to another broad genus of nucleic acid constructs for co-expression of a non-native polymerase and another nucleic acid sequence from the construct in a cell, again in any context, *in vivo* or *in vitro*. Dependent claims include the limitations: (1) a recognition site for the polymerase, (2) where the recognition site is complementary to a primer for the polymerase, (3) where the primer is tRNA, (4) where the polymerase is DNA polymerase,

RNA polymerase, reverse transcriptase, or a combination, (5) where the RNA polymerase is a bacteriophage RNA polymerase, either T3, T7, SP6 or a combination, (6) a promoter for the RNA polymerase, (7) the nucleic acid produced is DNA, RNA, or a hybrid, chimera, or a combination and is sense or antisense DNA or RNA.

Claims 245-246 are broadly drawn to a construct for production of a product in a cell having a tail hybridized to an antibody and also having a covalently or hydrophobically bound entity with a chemical modification or a ligand.

Claims 247-266 are drawn to a composition having a "non-natural entity" of two "domains," one to a nucleic acid and the second to a cell of interest, and where the domains are not the same. The dependent claims further specify: (1) a binder which can or cannot be the same as one of the domains, and can be a polymer, matrix, support, or combination, (2) the nucleic acid can be a single nucleic acid, a nucleic acid construct, conjugate, virus, viral fragment, viral vector, viroid, phage, plasmid, vector, bacterium and fragment, or combination, (3) the domains can be attached covalently, non-covalently, or through a binder or a combination, (4) interaction with a ligand binding receptor (see claim 258), (5) binder attached by a "means other than a natural binding site" and consisting of modified fibronectin or polylysine or both, (6) and methods and a kit for administering the parent composition to a cell *in vivo* and *ex vivo*.

Claims 267-284 are drawn to an analogous invention as that of claims 247-266 but specifying "an entity" having "at least one domain to a cell of interest" attached to a non-double stranded nucleic acid component.

Claims 285-302 are further drawn to an analogous invention as that of claims 247-284, but specifying "an entity" having "a domain to a nucleic acid component wherein said domain is attached to a cell of interest."

The specification teaches several constructs designed for entry into a cell and expression of one or more sequences to perform a biological function such as antisense inhibition of a nucleic acid. Specifically, several CHENAC constructs are taught prophetically, and pictured in figures 1-13 as vector based constructs constructed by using modified nucleic acid regions and designed to provide improved entry into a cell by way of improved construct-cell interaction. A second group of nucleic acid fused with antibody based constructs are taught prophetically and shown in figures 14-21. Preparation of multimeric insulin by means of nucleic acid hybridization is further taught prophetically and shown in figures 22-23. No exemplification for such constructs is taught in the specification as filed.

Furthermore, vectors ultimately designed for antisense inhibition of HIV in cells by co-expression of antisense DNA under control of a T7 promoter with a T7 polymerase (represented in figures 24-49) are taught and supported by *in vitro* data. Specifically, construction of the M13 phage vectors pRT-A, pRT-B, and pRT-c are taught which contain the coding sequence for the T7 RNA polymerase driven by the RSV promoter and with an SV40 intron sequence that will be spliced out to form a functional polymerase enzyme and each respective construct also having the antisense A, B, and C sequences driven by a T7 promoter and terminated by a T7 terminator. A modified version of the pINT-3 construct (the parent vector of pRT-A, B and C vectors before

insertion of the antisense sequences) is taught where a polylinker is inserted behind the poly-A tail of the T7 polymerase gene for subsequent sub-cloning of the lacZ gene in this instance to form pINT-LacZ. The result upon introduction in a eukaryotic cell would be synthesis of the T7 polymerase from the RSV promoter which in turn acts upon the T7 promoter to synthesize B-galactosidase.

Furthermore, plasmids are taught containing anti-sense segments introduced into the transcript region of the U1 gene, plasmid pHSD-4 U1 so that upon expression of the transcript, the antisense RNA sequence is produced to the complementary region of the HIV genome. Specifically, pDU1-A, B, C and D were made using the antisense A, B, and C sequences previously described and D as a control containing a non-HIV sequence. A multi-cassette version of the constructs was also made by sub-cloning in tandem the A,B, and C antisense to make pNDU1 (A,B,C) (N meaning the construct was also contained the gene for neomycin resistance).

Other multi-cassette constructs taught were:

(1) TRI 101, an M13 phage vector containing the "A" antisense T7 operon , the "B" antisense T7 operon and the "C" antisense T7 operon in a single construct (figure 46). Co-transfection would be required for expression of the antisense molecules from this construct with a vector that expresses T7 RNA polymerase (suggested is the intron containing construct of example 19); and,

(2) an M13 construct constructed from a multi-ligation of portions of pINT-3 (containing the intron containing polymerase) and the T7 promoter driven A, B, and C sequences (see figure 47).

The specification teaches application of some of these constructs ("various U1 constructs described above" p. 167, last line) in antisense inhibition of HIV in infected U937 cell culture. Specifically the following is shown: (1) expression of A, B, and C antisense by hybridization analysis after expression of the "U1 clone" (p. 169, line 3), (2) expression of the "triple U1 construct" (p. 169, para. (c), line 1) which result in a decrease in p24 production next to the control, and increased % reduction in p24 over time and after re-infection of cells, and these results were confirmed by absence p24 amplification next to control cells via PCR of the targeted DNA, and (3) expression of the construct of figure 50, a fusion product antisense A upstream of B-gal gene where antisense activity of the A portion caused inhibition of B-gal activity as shown in lacZ assays. The results in figure 51 show HIV A/Anti-A activity and HIV A/Anti-ABC (when the triple U1 construct was used by *co-transfection*) as the equivalent of the uninfected cells whereas the infected and control containing cells showed high B-gal expression. Therefore, it does not appear in the specification as filed that the multi cassette A,B,C and T7 polymerase construct (expressed on same plasmid) was applied to the same HIV challenge experiments.

Additional constructs are more prophetically taught: the primary nucleic acid construct that propagates production centers for the production of single-stranded antisense, etc. in

examples 21-25, and the retro virus vector containing sequences for the expression of antisense RNA directed at HIV on page 181, last para.

Claims 22-24 read on any construct bound non-ionically to a ligand or otherwise chemically modified entity, further limited as having a polynucleotide tail terminus and where the tail is hybridized to a complementary polynucleotide sequence. Likewise, claims 245-302 read on any construct for production of a product in a cell having (1) a polynucleotide terminus bound to an antibody, and having an entity comprising a chemical modification or ligand bound to the construct, or (2)"entities" having "domains" with nucleic acid and/or cell "components." The breadth of genus sought for such is not enabled in view of the lack of specificity of guidance in the specification as filed. The specification fails to provide guidance for the breadth claimed since the claims vaguely claim "constructs" which "produce products." The specification does not teach by example, other than prophetically, use of any nucleic acid constructs having one or more domains for cell interaction (claims 247-302), nor methods or kits for using such a construct. Nor does it teach a construct with a polynucleotide tail with an antibody bound and also bound to an entity having a chemical modification or a ligand (claims 245-246). The specification teaches only by way of example HIV inhibition by antisense expression from vector constructs which do not entail chemical modified entities nor polynucleotide termini.

Furthermore, the claims specify the context for producing the product in a cell and no exemplification of whole organism success is found in the specification as filed. There is a high level of unpredictability in the antisense art and analogous gene therapy art for *in vivo* (whole

organism) applications. The factors considered barriers to successful delivery of antisense delivery to the organism are: (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or nucleus, (2) withstanding enzymatic degradation, and (3) the ability to find and bind the target site and simultaneously avoid non-specific binding (see Branch). Despite the synthesis of more resilient, nuclease resistant, oligonucleotide backbones and isolated successes with antisense therapy *in vivo*, the majority of designed antisense molecules still face the challenge of successful entry and localization to the intended target and further such that antisense and other effects can routinely be obtained. Note Flanagan et al. who teach "although numerous reports have cited antisense effects using oligonucleotides added to cell medium, direct proof that oligonucleotides enter cells and affect gene inhibition by an antisense mechanism is still lacking (page48, column 1)."

Specifically, *in vitro* results with one antisense molecule are not predictive of *in vivo* (whole organism) success. *In vitro*, antisense specificity to its target may be manipulated by "raising the temperature or changing the ionic strength, manipulations that are commonly used to reduce background binding in nucleic acid hybridization experiments." (Branch, p. 48) Discovery of antisense molecules with "enhanced specificity" *in vivo* requires further experimentation for which no guidance is taught in the specification. Note Branch who teaches the state of the art for designing an antisense which inhibits a target *in vivo:* it "is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells (Branch,

p.49)." And in the instant case, the claims read broadly on administration of an antisense inhibitor in any cell, therefore the whole organism included. While the specification teaches cell culture inhibition, no evidence of successful *in vivo* (whole organism) antisense inhibition has been shown, nor do the culture examples correlate with whole organism delivery.

One of skill in the art would not accept on its face the successful delivery of the disclosed antisense molecules *in vivo* in view of the lack of guidance in the specification and the unpredictability in the art. Specifically the specification does not teach (1) stability of the antisense molecule *in vivo*, (2)effective delivery to the whole organism and specificity to the target tissues, (3) dosage and toxicity, nor (4) entry of molecule into cell and effective action therein marked by visualization of the desired treatment effects. These key factors are those found to be highly unpredictable in the art as discussed *supra*. The lack of teaching of these factors in inhibition of the target, coupled to the amount of "trial and error" experimentation involved in the deduction of these results would lead one skilled in the art to necessarily practice an undue amount of experimentation *in vivo*.

No determination of enablement can be made for claims 2-21 because there is no independent claim from which they depend. Without knowing what claims 2-21 depend on, the full scope of the claims is not known.

8. Claims 2-24 and 245-262, 267-280, and 285-298 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way

as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 2-21 are drawn to a missing independent claim and therefore the scope claimed is not able to be determined. Claims 22-24 are drawn to a broad scope of constructs which are bound non-ionically to an entity having a chemical modification or a ligand and produce a product in a cell. Claims 245-302 are further drawn to a broad scope of constructs for production of a product in a cell having (1) a polynucleotide terminus bound to an antibody, and having an entity comprising a chemical modification or ligand bound to the construct, or (2)"entities" having "domains" with nucleic acid and/or cell "components."

The claims broadly encompass "constructs" for producing a "product," or "entities" having "domains" to nucleic acid components and cell components, and it is not clear what is embraced by the claims. The claims read on vectors, genomes, cell processes like translation, transcription, etc. as "constructs" for producing "products." The language "domain" in reference to nucleic acid constructs and cells reads on *any* region distinctively marked by some physical feature of the nucleic acid or cell. For example, the region may encompass the whole cell or a small component such as a ligand binding site to one receptor. Furthermore, the scope of "chemical modification" as used in claims 22 and 245 is not clear in relation to the construct.

The instant specification describes prophetically a number of potential modified nucleic acid constructs for expression of an entity in a cell. The supporting figures provide limited additional disclosure of relevant identifying structural characteristics because they primarily

correspond to expression vector based constructs which are only one facet of the invention in light of the nebulous scope claimed.

Clearly the specification only considers vector-like constructs for delivery and expression of nucleic acids. Specifically, for claims 245-302, no vector nucleic acid constructs having antibodies or cellular "domains" are described by way of example except by prophetically.

Despite the known predictability of standard vector construction in the molecular biology art, in view of the nearly infinite scope claimed and the lack of adequate description in the specification for such a broad genus of possible "constructs," coupled with the high level of unpredictability for constructs which could fall within this genus such as those involving gene therapy, the specification as filed fails to provide one skilled in the art enough description to show possession of a representative number of "construct" species for the breadth claimed.

See the June 15, 1998 (Vol. 63, No. 114, Pages 32639-32645) Federal Register for the interim guidelines for the examination of patent applications under the 35 U.S.C. 112 "Written Description" requirement.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

10. Claims 245-302 are rejected under 35 U.S.C. 102(e) as being anticipated by Curiel et al.

The claimed invention is drawn to: (1) constructs for production of a product in a cell having a terminus, a polynucleotide tail, and an entity comprising a chemical modification or a ligand bound to the construct, (2) constructs having two domains, one a nucleic acid and one a domain to a cell of interest and methods and kits for introduction of said construct into a cell or organism, (3) a composition having at least one domain to a cell of interest attached to a nucleic acid in non-double stranded form and methods and kits for introduction into a cell or organism, and (4) a composition having one domain to a nucleic acid component attached to a cell of interest and methods and kits for introduction into a cell or organism.

Curiel et al. teach constructs for improved nucleic acid delivery into cells (and organisms) for production of a product (for example, antisense or ribozymes, col.1, line 65) including adenovirus-antibody-polylysine-DNA complexes (see fig 1) which therefore have the potential to complex as 'domains'.

11. Claims 22-24 are rejected under 35 U.S.C. 102(e) as being anticipated by Meyer et al..

The claimed invention is drawn to any construct which when present in a cell produces a product, and is bound non-ionically to an entity comprising a modification or a ligand, and further comprises a hybridized polynucleotide tail.

Meyer et al. teach a covalently linked conjugate of an oligonucleotide (ODN) with a peptide and a carrier or targeting ligand (ODN-peptide-carrier) including a therapeutic oligonucleotide which is capable of selectively binding to a target sequence of DNA, RNA or protein inside a target cell. The invention of Meyer et al. Reads on all of the instant claimed limitations for a non-naturally occurring construct for production of a product in a cell (in Meyer, an antisense oligonucleotide is produced).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *George Elliott, Ph.D.* may be reached at (703) 308-4003. The examiner's primary, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JOHN L. LeGUYADER
PRIMARY EXAMINER
GROUP ~~1800~~ 1600